

## SYNTHESIS ARTICLE – ARTICLES DE SYNTHÈSE



### HELICOBACTER PYLORI – RISK FACTOR FOR GASTRIC CANCER

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#### ABSTRACT

|                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Introduction</b>         | Over the last 7-8 decades, a global average annual percentage reduction of 2.1% in gastric cancer has been reported, partly due to the effective eradication and decreased prevalence of <i>Helicobacter pylori</i> infection, particularly among younger age cohorts, along with improved dietary habits and cancer screening.                                                                                                                                                                                                   |
| <b>Material and methods</b> | Publications were selected from the <i>PubMed</i> , <i>Hinari</i> , <i>SpringerLink</i> , and <i>Google Search</i> databases using the keyword " <i>Helicobacter pylori</i> " in various combinations with the terms "gastric cancer" and "carcinogenesis" to maximize the search yield. In the final bibliography, 36 representative articles were included for the purposes of this synthesis.                                                                                                                                  |
| <b>Results</b>              | Inflammation is the most important and frequent factor in <i>Helicobacter pylori</i> -induced carcinogenesis. Chronic inflammation induces cancer by increasing the production of reactive oxygen species leading to oxidative stress, apoptosis of epithelial cells with a compensatory proliferative response of the remaining cells, and a higher risk of mutations in proliferating epithelial cells. In addition, <i>Helicobacter pylori</i> impairs DNA repair, causing epigenetic alterations in gastric epithelial cells. |
| <b>Conclusions</b>          | The pathogenesis of gastric cancer includes a sequence of events starting with <i>Helicobacter pylori</i> -induced chronic superficial gastritis, progressing to chronic atrophic gastritis, gastric intestinal metaplasia, gastric epithelial dysplasia, and ultimately gastric cancer.                                                                                                                                                                                                                                          |
| <b>Keywords</b>             | Risk factors, <i>Helicobacter pylori</i> , gastric cancer, epidemiology, virulence, inflammation.                                                                                                                                                                                                                                                                                                                                                                                                                                 |

#### HELICOBACTER PYLORI – FACTOR DE RISC AL CANCERULUI GASTRIC

|                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Introducere</b>        | În ultimele 7-8 decenii a fost raportată o reducere procentuală medie anuală globală a cancerului gastric de 2,1%, parțial din cauza eradicării eficiente și reducerii prevalenței infecției cu <i>Helicobacter pylori</i> , îndeosebi în cohortele de vârstă mai tânără, obiceiurilor alimentare mai bune și screening-ului cancerului.                                                                                                                                                                                               |
| <b>Material și metode</b> | Publicațiile au fost selectate din bazele de date <i>PubMed</i> , <i>Hinari</i> , <i>SpringerLink</i> și <i>Google Search</i> utilizând cuvintele-cheie: „ <i>Helicobacter pylori</i> ” folosit în diferite combinații cu cuvintele „cancer gastric” și „carcinogeneză” pentru a maximiza randamentul căutării. În bibliografia finală a lucrării au fost incluse 36 de articole reprezentative pentru scopul acestui articol de sinteză.                                                                                              |
| <b>Rezultate</b>          | Inflamația este cel mai important și frecvent factor în procesul carcinogenezei induse de <i>Helicobacter pylori</i> . Inflamația cronică induce cancer prin creșterea producției de specii reactive de oxigen care duc la stres oxidativ, apoptoza celulelor epiteliale cu un răspuns proliferativ compensator al celulelor rămase și creșterea riscului de mutații în celulelor epiteliale în proliferare. În plus, <i>Helicobacter pylori</i> afectează repararea ADN-ului cu alterări epigenetice în celulele epiteliale gastrice. |
| <b>Concluzii</b>          | Patogenia cancerului gastric include o secvență de evenimente care începe cu gastrita cronică superficială, indusă de <i>Helicobacter pylori</i> , progresând spre gastrită cronică atrofică, metaplazie intestinală gastrică, displazia epitelului gastric și cancer gastric.                                                                                                                                                                                                                                                         |
| <b>Cuvinte-cheie</b>      | Factori de risc, <i>Helicobacter pylori</i> , cancer gastric, epidemiologie, virulență, inflamație.                                                                                                                                                                                                                                                                                                                                                                                                                                    |

## INTRODUCTION

Over the past 7-8 decades, a global average annual percentage reduction of 2.1% in gastric cancer (GC) has been reported (1). This positive trend is partly attributed to the effective eradication and decreased prevalence of *Helicobacter pylori* (HP) infection, especially among younger age groups, as well as the adoption of healthier dietary habits and regular cancer screening. Nevertheless, GC remains one of the most widespread types of malignancies worldwide, with marked global variability, accounting for 5.5% of all new cancer cases. Moreover, according to recent statistics, GC is the fourth most lethal cancer globally, responsible for 7.7% of total cancer deaths. The highest incidence rates are found in East Asia, while lower incidence rates are observed in North America, Northern Europe, and Africa. The incidence of GC is approximately twice as high in men compared to women, and in recent years, increasing rates have been reported among younger patients (under 50 years of age) (2, 3, 4, 5).

According to GLOBOCAN 2018 data, the cumulative lifetime risk (up to the age of 74) of GC incidence worldwide was 1.87% among men and 0.79% among women, with higher rates in the Western Pacific region (1, 3, 6). According to study results, the vast majority of GC cases (approximately 75% of all new GC cases and about 80–90% of new non-cardia GC cases) are associated with HP infection, and more than 70% of the total number of GC cases occur in developing countries (7).

These changes in the epidemiology of GC justify further research and cancer control measures, with primary and secondary prevention as the main goal, given the poor prognosis in many parts of the world (5). Preventing HP infection and ensuring its timely eradication (before the development of extensive atrophic changes) are the most effective strategies for preventing the development of precancerous gastric lesions and for the primary prevention of GC. An attractive proposal for reducing the incidence of the disease is to identify individuals at high risk who may benefit from screening, as well as from prophylactic and therapeutic measures aimed at preventing the onset of malignancy (8, 9, 10).

In this context, the aim of the article is to develop a narrative synthesis of contemporary studies in order to review current concepts regarding *Helicobacter pylori* infection as a risk factor for gastric cancer, with a view to establishing strategies for the prevention of this disease. We will highlight the main mechanisms through which HP can lead to GC: indirectly, through inflammatory processes, and directly, through its action on gastric epithelial cells.

## MATERIAL AND METHODS

To achieve the stated objective, an initial comprehensive search of scientific publications was carried out, using the *PubMed*, *Hinari (Health Internet Work Access to Research Initiative)*, *SpringerLink*, *National Center for Biotechnology Information*, and *Medline* databases. A combination of Boolean operators and keywords was used to identify rel-

evant studies. The article selection criteria included contemporary data on HP infection as a risk factor for GC, based on the following keywords: “*Helicobacter pylori*,” “risk factors,” “cancer,” “gastric cancer,” and “carcinogenesis.” To maximize the search yield, the following Boolean operators were applied:

- “*Helicobacter pylori*” OR “risk factors” AND “cancer”
- “*Helicobacter pylori*” OR “risk factors” AND “gastric cancer”
- “*Helicobacter pylori*” OR “risk factors” AND “carcinogenesis.”

For the advanced selection of bibliographic sources, the following filters were applied: full-text articles, articles in English, and articles published between 2000 and 2024. After a preliminary analysis of the titles, original articles, editorials, narrative reviews, systematic reviews, and meta-analyses containing relevant information and contemporary concepts regarding HP infection as a risk factor for GC were selected. Additionally, the reference lists of the identified sources were searched to highlight further relevant publications that were not found during the initial database search.

A total of 36 studies were analyzed, including 4 retrospective cohort studies, 1 prospective, randomized, placebo-controlled study, 1 prospective observational cohort study, 29 narrative literature reviews, and 1 systematic review and meta-analysis (Table 1).

In order to minimize the risk of systematic errors (bias) in the study, we conducted thorough database searches to identify the maximum number of publications relevant to the study objective, evaluated only studies that met validity criteria, and applied strict exclusion criteria for articles.

Studies were included if they met the following criteria:

1. Comparison of the regional prevalence of HP infection with the incidence of GC in order to examine the association between these diseases.
2. Evaluation of the presence and effects of HP in healthy individuals, in patients with precancerous gastric lesions, and in those with GC.
3. Association of HP infection with the occurrence of GC, based on the detection of anti-HP antibodies in serum or the detection of the bacteria in biopsy specimens or surgical samples from patients with GC.
4. The effect of HP eradication on GC incidence.

**Table 1. Analysis of articles on *Helicobacter pylori* infection as a risk factor for gastric cancer.**

| No. | Authors, Year, Country                  | Type                         | Population | Main Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----|-----------------------------------------|------------------------------|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1.  | Scheiman J. et al., 1999, USA           | Systematic literature review | -          | The mechanisms of HP-induced carcinogenesis are independent. HP induces chronic inflammation and oxidative stress, which can damage DNA and promote carcinogenesis.                                                                                                                                                                                                                                                                                                                                                                                |
| 2.  | Alexander G. et al., 2000, USA          | Systematic literature review | -          | HP is classified as a Group 1 carcinogen.<br><br>The association between HP and GC is based on epidemiological studies, the detection of anti-HP antibodies in serum, or the detection of the bacterium in biopsy or surgical specimens from GC patients.                                                                                                                                                                                                                                                                                          |
| 3.  | Axon A., 2002, UK                       | Systematic literature review | -          | HP increases the relative risk of developing GC sixfold.<br><br>HP eradication can prevent GC incidence.                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 4.  | Correa P., 2003, USA                    | Systematic literature review | -          | Treatment of HP infection is recommended for infected individuals because of the high risk of GC.                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 5.  | Matysiak-Budnik T. et al., 2006, France | Systematic literature review | -          | The association between HP and GC is supported by experimental data showing HP's ability to induce GC in animals and by interventional studies demonstrating that HP eradication can reduce the risk of GC and prevent the development of precancerous gastric lesions in humans and experimental animals.<br><br>Mechanisms through which chronic inflammation leads to epithelial and precancerous lesions include induction of oxidative stress, disruption of the proliferation/apoptosis balance in epithelial cells, and cytokine secretion. |
| 6.  | Fuccio L. et al., 2007, Italy           | Systematic literature review | -          | Epidemiological studies have demonstrated a clear causal link between HP and GC.<br><br>HP eradication reduces the incidence of GC in patients without precancerous gastric lesions.<br><br>HP eradication is also reasonable for individuals with precancerous gastric lesions and a family history of GC.                                                                                                                                                                                                                                        |

| No. | Authors, Year, Country         | Type                                          | Population | Main Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----|--------------------------------|-----------------------------------------------|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7.  | Herrera V. et al., 2009, USA   | Systematic literature review                  | -          | <p>The proportion of GC in the population that would not occur in the absence of HP has been estimated at 75%. HP is responsible for up to 5.5% of all GC worldwide.</p> <p>HP-induced inflammation promotes cancer by increasing the production of free radicals, increasing apoptotic and necrotic epithelial resistance, inducing cell death, and promoting cell proliferation.</p> <p>HP interacts directly with epithelial cells, modulating proteins and activating genes.</p> |
| 8.  | Pandey R. et al., 2010, India  | Systematic literature review                  | -          | <p>There is a direct association between HP infection and GC.</p> <p>HP strains that are CagA-positive and VacA-positive present a much higher risk of developing GC.</p>                                                                                                                                                                                                                                                                                                            |
| 9.  | Polk D. et al., 2010, USA      | Systematic literature review                  | -          | <p>HP infection is the most important known risk factor for GC, with an attributable risk of approximately 75%.</p> <p>HP eradication significantly reduces the risk of developing GC in infected individuals without premalignant lesions, confirming the organism's role in the early stages of gastric carcinogenesis.</p>                                                                                                                                                        |
| 10. | Wroblewski L. et al, 2010, USA | Systematic literature review                  | -          | <p>A potential factor contributing to the inflammation-carcinoma sequence is the generation of oxidative stress. Oxidative DNA damage induced by HP infection has been well documented in gastric tissues.</p> <p>The CagA oncoprotein is one of the most significant determinants of HP virulence, contributing to gastric carcinogenesis.</p>                                                                                                                                      |
| 11. | IARC, 2013, France             | Systematic literature review (expert opinion) | -          | <p>HP is classified as a Group 1 carcinogen. Approximately 89% of non- cardia GC cases and 78% of all GC cases are attributed to chronic HP infection.</p> <p>HP treatment reduces GC incidence by 30–40% and also decreases the incidence of metachronous GC.</p>                                                                                                                                                                                                                   |

| No. | Authors, Year, Country             | Type                                           | Population | Main Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----|------------------------------------|------------------------------------------------|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12. | Ishaq S. et al., 2015, UK          | Systematic literature review                   | -          | <p>Infecția cu HP predispune indivizii la adenocarcinom gastric. Efectele oncogene ale HP pot apărea printr-o varietate de mecanisme, inclusiv efectele inflamatorii indirecte ale HP asupra mucoasei gastrice și efectele epigenetice directe ale HP asupra celulelor gastrice. Two important bacterial virulence factors of HP are CagA and VacA.</p> <p>Controversies remain regarding the impact of HP eradication on preventing the progression of gastric lesions and the possibility of regression of atrophic gastritis.</p> |
| 13. | Mégraud F. et al., 2015, France    | Systematic literature review                   | -          | <p>In addition to long-term inflammation, the HP oncoprotein CagA is involved in the carcinogenic process.</p> <p>HP can induce GC indirectly through inflammatory processes and directly by acting on gastric epithelial cells via the CagA protein.</p>                                                                                                                                                                                                                                                                            |
| 14. | Loor A. et al., 2016, Romania      | Systematic literature review                   | -          | <p>HP infection is clearly correlated with gastric carcinogenesis. HP is estimated to be responsible for 5.5% of all cancer cases and more than 60% of GC cases.</p>                                                                                                                                                                                                                                                                                                                                                                 |
| 15. | Moss S., 2016, USA                 | Systematic literature review                   | -          | <p>The majority of non-cardia GC cases are attributable to HP infection.</p> <p>Screening and HP eradication in areas with a high GC prevalence reduce the risk of GC by half.</p>                                                                                                                                                                                                                                                                                                                                                   |
| 16. | Talebi Bezmin Abadi A., 2016, Iran | Systematic literature review                   | -          | <p>Certain HP strains increase GC risk to different degrees. CagA, secreted by the bacteria and responsible for inducing high levels of chronic inflammation, is the main factor increasing mutagenesis rates, oxidative stress, and the activation of error-repair pathways, leading to gastric carcinogenesis.</p> <p>HP eradication reduces bacterial effects relevant to GC.</p>                                                                                                                                                 |
| 17. | Seta T. et al., 2017, Japan        | Systematic literature review and meta-analysis | -          | <p>HP infection is strongly associated with the occurrence of GC.</p> <p>The efficacy of HP eradication therapy in suppressing primary GC occurrence was significant.</p>                                                                                                                                                                                                                                                                                                                                                            |

| No. | Authors, Year, Country              | Type                                                            | Population                                                                                                                 | Main Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----|-------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18. | Ari A. et al. 2018, Turkey          | Retrospective cohort study                                      | 60 GC patients                                                                                                             | HP is one of the etiological factors of GC.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 19. | Díaz P. et al., 2018, Chile         | Systematic literature review                                    | -                                                                                                                          | HP infection is the main risk factor associated with the development of GC. HP promotes chronic inflammation and oxidative stress, leading to primary tissue damage.                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 20. | Mentis A. et al., 2019, Switzerland | Systematic literature review                                    | -                                                                                                                          | HP infection is a critical risk factor for GC, contributing to approximately 75% of all GC cases.<br><br>The CagA protein plays a role in GC in adults.                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 21. | Choi I. et al., 2020, South Korea   | Prospective, randomized, double-blind, placebo-controlled study | 1,676 HP-positive patients (first-degree relatives of GC patients): 832 received eradication therapy; 844 received placebo | Over a median follow-up period of 9.2 years, GC developed in 1.2% of patients in the treatment group and 2.7% in the placebo group ( $p = 0.03$ ).<br><br>HP eradication reduced GC incidence, with effects observed even among individuals with a first-degree family history of GC.                                                                                                                                                                                                                                                                                                                                            |
| 22. | Liou J. et al., 2020, Taiwan        | Systematic literature review                                    | -                                                                                                                          | At the individual level, HP eradication reduces GC risk in asymptomatic subjects and is recommended. In vulnerable cohorts (first-degree relatives of GC patients), a screening and treatment strategy is also beneficial. HP eradication in patients with early GC after curative endoscopic resection reduces the risk of metachronous cancer.<br><br>At the population level, screening and treatment for HP infection is the most cost-effective strategy among young adults in regions with high GC incidence and is recommended preferably before the development of chronic atrophic gastritis and intestinal metaplasia. |
| 23. | White J. et al., 2020, UK           | Systematic literature review                                    | -                                                                                                                          | GC develops through a gradual progression from normal mucosa to adenocarcinoma, most commonly triggered by HP infection.<br><br>HP eradication reduces subsequent GC risk. This benefit is not consistently maintained in patients with gastric intestinal metaplasia or dysplasia.                                                                                                                                                                                                                                                                                                                                              |

| No. | Authors, Year, Country                         | Type                                              | Population                                                                                             | Main Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----|------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24. | Adeeb AT., 2021, Iraq                          | Systematic literature review                      | -                                                                                                      | HP is the strongest risk factor for GC. Treatment of this bacterium can prevent GC development.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 25. | Piscione M. et al., 2021, Italy                | Systematic literature review                      | -                                                                                                      | GC, particularly antral cancer, is linked to HP infection. The progression of HP infection through chronic active gastritis has been demonstrated.<br><br>The CagA virulence factor, inflammation, and oxidative stress are essential in the development of HP-induced carcinogenesis.                                                                                                                                                                                                                                                                                                                           |
| 26. | Joshi S. et al., 2021, USA                     | Systematic literature review                      | -                                                                                                      | HP infection is a major risk factor for GC.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 27. | Matysiak-Budnik T., 2021, France               | Systematic literature review                      | -                                                                                                      | HP eradication is always beneficial, but to achieve the greatest effect, it should be performed in young adults.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 28. | Senchukova M. et al., 2021, Russian Federation | Prospective observational cohort study            | 109 GC patients                                                                                        | HP is involved not only in the initiation and development but also in the progression of GC.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 29. | Yan L. et al., 2022, Sweden                    | Prospective, randomized, placebo-controlled study | 1,630 asymptomatic HP-infected individuals: 817 received standard triple therapy; 813 received placebo | Over 26.5 years of follow-up, 21 participants (2.57%) in the treatment arm and 35 (4.31%) in the placebo arm were diagnosed with gastric cancer.<br><br>HP eradication may provide long-term protection against GC in high-risk populations, particularly in infected individuals without precancerous gastric lesions.                                                                                                                                                                                                                                                                                          |
| 30. | Kesharwani A. et al., 2023, India              | Systematic literature review                      | -                                                                                                      | HP is the main factor responsible for GC pathogenesis. The coexistence of a genetically susceptible host, a virulent bacterial strain, and a sensitized gastric environment can contribute to cancer development.<br><br>The most important pathogenic components of HP virulence are the CagA and VacA cytotoxins.<br><br>The mechanisms through which HP leads to GC development include chronic inflammation, DNA damage, suppression of the host immune system, anti-apoptotic activity, production of oxidative stress contributing to chronic inflammation, mutation accumulation, and cancer progression. |



| No. | Authors, Year, Country              | Type                                                          | Population                                                                                           | Main Findings                                                                                                                                                                                                                                                                                                                             |
|-----|-------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 31. | Reyes V., 2023, USA                 | Systematic literature review (or narrative literature review) | -                                                                                                    | HP is the primary risk factor involved in the development of GC. HP infection induces chronic inflammation that affects the gastric epithelium, leading to DNA damage and the promotion of precancerous lesions.<br><br>CagA oncoprotein is one of the most important determinants of <i>Helicobacter pylori</i> virulence in host cells. |
| 32. | Salvatori S. et al., 2023, Italy    | Systematic literature review                                  | -                                                                                                    | HP is one of the main risk factors for GC. The carcinogenic mechanisms associated with HP are based on the onset of chronic inflammation (oxidative stress) and on specific bacterial virulence factors (CagA, VacA), which can damage the DNA of gastric epithelial cells and promote genomic instability.                               |
| 33. | Usui U. et al., 2023, Japan         | Retrospective cohort study                                    | 1,433 GC patients and 5,997 control individuals                                                      | Patients with HP infection had a higher cumulative risk of GC than non-carriers of the infection.                                                                                                                                                                                                                                         |
| 34. | Kouroumalis E. et al., 2024, Greece | Systematic literature review                                  | -                                                                                                    | HP strains producing the CagA and VacA cytotoxins are more dangerous in initiating GC.<br><br>HP eradication should be reserved for specific patient groups, such as first-degree relatives of GC patients.                                                                                                                               |
| 35. | Yoo H. et al., 2024, South Korea    | National retrospective cohort study                           | 69,722 patients with endoscopically treated gastric dysplasia; 49.5% received HP eradication therapy | HP eradication after endoscopic resection of gastric dysplasia was associated with a reduced risk of both primary and metachronous GC.                                                                                                                                                                                                    |
| 36. | Zhao Z. et al., 2024, China         | Retrospective cohort study                                    | 1,293 GC patients after radical gastrectomy (125 with anti-HP treatment; 1,168 without)              | Patients receiving anti-HP treatment had a significant advantage in terms of overall survival and disease-free survival compared to those without HP treatment.                                                                                                                                                                           |

The information from the publications included in the bibliography was collected, classified, evaluated, and synthesized, highlighting the main aspects of the contemporary understanding of *Helicobacter pylori* infection as a risk factor for gastric cancer. Particular attention was paid to the type of study (retrospective, cohort, prospective, cross-sectional, case-control), the number of patients included in each study, and the detection methods used.

When necessary, additional information sources were consulted to clarify certain concepts. Duplicate publications, articles that did not correspond to the purpose of the study, and those that were not available for full-text viewing were excluded from the list of publications generated by the search engine.

## RESULTS

Following the processing of information identified from the *PubMed*, *Hinari*, *SpringerLink*, *National Center for Biotechnology Information*, and *Medline* databases according to the search criteria, a total of 246 full-text articles addressing the role of HP infection in the development of GC were found. After a detailed analysis of eligibility, titles, and abstracts, 60 duplicate articles and those without full-text versions were excluded, as well as 95 articles for not meeting the inclusion criteria and 55 articles for irrelevant details and/or insufficient methodology. Ultimately, 36 publications considered representative of the materials published on this topic were selected and included in the final bibliography (Fig. 1). The search and selection of publications were carried out by the author.

**Definition:** *Helicobacter pylori* is a Gram-negative, spiral-shaped, flagellated bacterium that selectively colonizes the semi-permeable gastric mucus gel layer covering the apical surface of the gastric epithelium (4). Approximately 20% of the bacteria attach to gastric epithelial cells, thereby evading the immune response. Researchers have identified HP in the cytoplasm of epithelial cells, in intercellular spaces, in the lamina propria of the gastric mucosa, and in the lumen of small vessels (11, 12).

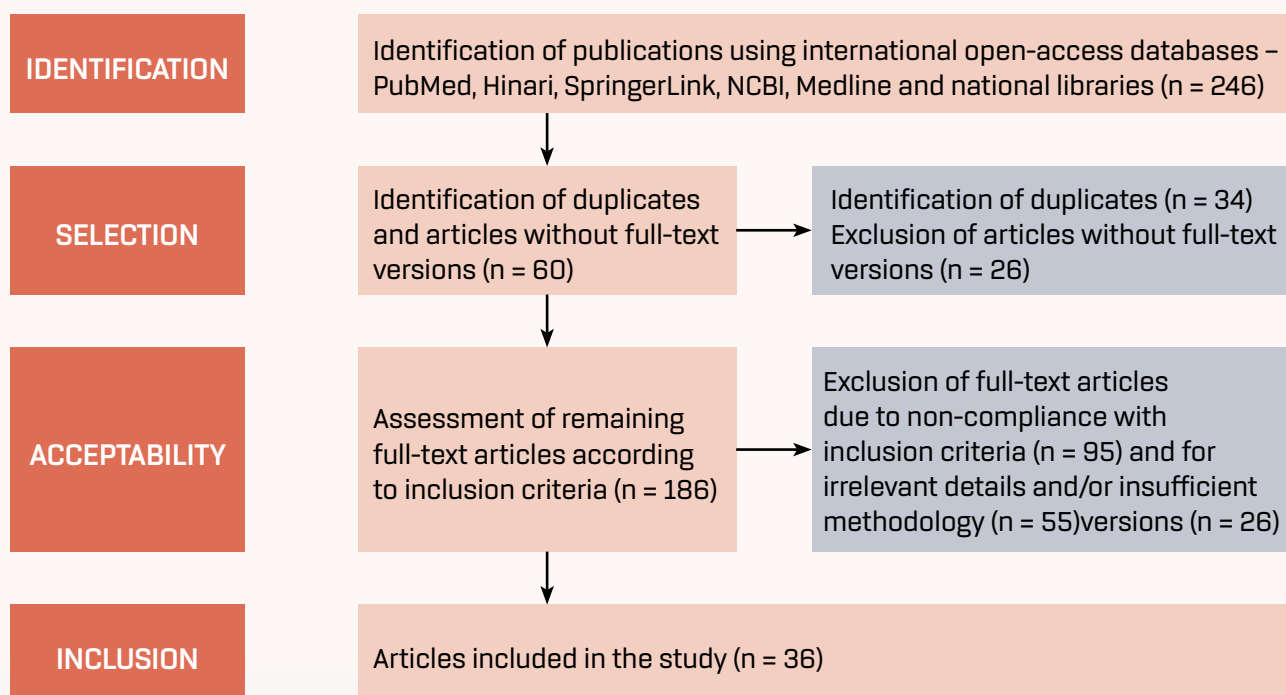


Figure 1. Literature search algorithm.

HP causes the most common bacterial infection worldwide. HP has developed mechanisms that enable it to colonize the highly acidic gastric environment by metabolizing urea into ammonia through urease, which is abundantly produced by the bacterium. This process creates a local microenvironment with a neutral pH. In most cases, the infection is asymptomatic and is universally associated with chronic or acute inflammation and, at times, with other types of gastric lesions, including gastric ulcers, mucosa-associated lymphoid tissue, chronic atrophic gastritis, and gastric intestinal metaplasia. Antimicrobial therapy leads to the regression of inflammation over time (13, 14, 15, 16, 17, 18, 19, 20).

HP differs from other bacteria through a set of properties that enable it to colonize the gastric mucosa and persist for long periods under conditions that are unfavorable for other microorganisms. These include: (1) the ability to produce a special enzyme – urease; (2) the synthesis of lytic enzymes that cause the depolymerization and dissolution of gastric mucus, which consists mainly of mucin; (3) the bacterium's mobility, ensured by the presence of 5-6 flagella; (4) the high adhesiveness of the bacteria to the epithelial cells of the gastric mucosa; (5) the production of various exotoxins (VacA, CagA, and others); (6) the instability of the HP genome; (7) the presence of the bacterium in both vegetative and biofilm forms; and (8) the ability to persist intracellularly and translocate beyond the gastric mucosa (11).

### *Epidemiology*

HP is usually acquired in childhood, most commonly before the age of 10, leading to an infection that persists throughout life. Currently, an average of 50% of the world's population is infected with HP. Transmission occurs largely from person to person via the fecal-oral or gastric-oral route within families, particularly in settings with poor sanitation and hygiene. However, the bacterium is commensal and harmless for the vast majority of the infected population (1, 3, 6, 13, 15, 21).

The prevalence of infection varies worldwide depending on the geographical distribution and the socioeconomic status of the population. This indicator is higher in developing countries (up to 80%) and significantly lower in economically developed countries (up to 30%) (1, 8, 13, 15, 17, 19, 21). However, there is a discrepancy between the prevalence of HP infection and GC rates in certain populations from Africa, India, and coastal areas of Latin America. These populations have high infection rates but low GC rates, a phenomenon largely unexplained and referred to as the "African enigma." This variation may possibly be explained by a combination of the following factors: age at acquisition of infection, HP strain type, host genetic profile, dietary habits, and environmental factors (8, 17, 19, 20, 22, 23).

### *Diagnosis*

HP infection can be defined through non-invasive methods (serological – detection of serum HP-IgG using enzyme-linked immunosorbent assay (ELISA) and immunoblotting, urea breath test, detection of HP antigen in stool samples) and invasive methods (histological examination of gastric biopsy specimens collected endoscopically and rapid urease testing) (2, 21).

### *Epidemiological relationships between GC and HP*

The major breakthrough in GC research came with the pioneering discovery of the HP bacterium by Barry Marshall and Robin Warren in 1983, the scientists who were the first to identify the relationship between HP infection in gastric tissue and gastritis and peptic ulcer disease (2, 6, 13, 14, 21, 23, 24). Since its initial description, HP has inspired intensive investigations aimed at better understanding its interactions with the human host at the cellular and molecular levels, as well as its pathogenic potential. Interest in HP as an etiological factor for gastric cancer arose following observations of a causal correlation between infection and the neoplastic process. The first studies examining the association between HP and GC compared the regional prevalence of HP infection with GC incidence. Subsequently, numerous epidemiological studies, systematic literature reviews, meta-analyses of case-control studies, and experimental models have confirmed the association between GC and HP infection. This close relationship has been observed between HP and both intestinal-type GC and diffuse-type GC (4, 10, 13, 20, 21, 23). It is generally accepted that the risk of GC is highest among patients in whom primary colonization with HP causes acute and then chronic inflammation (22).

Following the discovery of HP in the early 1980s, more than 1,000 studies have been conducted on the association between the bacterium and GC, including observational studies (ecological, case-control, and cohort), clinical studies on HP eradication, pathological studies, and experimental studies using animal models. The results largely confirmed the relationship between infection and malignancy. The most convincing observational evidence of the association between HP infection and GC comes from longitudinal cohort studies (13, 24, 25). Epidemiological data have shown that HP infection is associated with a 3- to 6-fold increased risk of developing non-cardiac GC, with GC progression, and with poorer long-term outcomes (11, 18, 19, 20, 21, 24, 26). Many studies have confirmed the association between HP infection and the occurrence of GC based on the detection of anti-HP antibodies in serum or the detection of the bacteria in biopsy specimens or surgical samples from GC patients. The results of surgical specimen studies increased HP positivity rates to as high as 90% (21). In addition, the prevalence of infection was statistically significantly higher among patients with the intestinal type (80-90%) compared to those with the diffuse type (30.0-31.8%) of GC. These results demonstrate a direct association between HP infection and the intestinal type of gastric carcinoma (19, 23, 24).

Among individuals infected with HP, approximately 10% develop peptic ulcers, 1-3% develop gastric adenocarcinoma, and 0.1% develop mucosa-associated lymphoid tissue (MALT) lymphoma (1, 6, 15, 23, 27, 28). A family history of GC in a first-degree relative is associated with a two- to threefold increased risk of GC (29).

Based on strong evidence supporting the etiological role of HP infection in GC, in 1994 the World Health Organization classified HP as a class I human carcinogen (a definite cause of human GC) (17, 18, 22).

At the population level, the “screen and treat” strategy for HP is the most cost-effective among young adults in regions with a high inci-

dence of GC and is recommended preferably before the development of chronic atrophic gastritis and gastric intestinal metaplasia (6, 21). A pilot study of mass screening and HP eradication in a population from an area with highly endemic HP infection and a high incidence of GC reported very promising initial results. Over a relatively short period of time, the authors observed a 78.7% reduction in HP infection, a 77.2% reduction in the incidence of gastric atrophy, a 25% reduction in GC incidence, and a 67.4% reduction in peptic ulcer incidence (24). Among HP-infected individuals with a family history of GC in first-degree relatives, eradication therapy reduced the risk of GC occurrence (29). A recent prospective, randomized, placebo-controlled study published in 2022, with 26.5 years of follow-up, along with other studies and meta-analyses, has provided strong evidence that HP eradication therapy may offer long-term protection against GC in high-risk populations, particularly in healthy, asymptomatic infected individuals without advanced gastric lesions at baseline (10, 12, 26, 30). However, HP eradication in patients with advanced preneoplastic gastric lesions does not prevent the development of GC, and endoscopic surveillance must always be performed (10).

Because HP eradication requires a large number of subjects and many years of follow-up, researchers have used GC precursors (multifocal atrophic gastritis and gastric intestinal metaplasia) as surrogates for measuring the effects of HP eradication on the malignant process. Overall, these studies suggest regression of preneoplastic gastric lesions, although the change is slow and not universally observed. Thus, the studies conducted support an unequivocal role for HP infection in the development of GC and indicate that eradication of the infection may be an effective means of preventing both primary and metachronous GC (10, 13, 14, 15, 30, 31, 32).

Thus, HP infection is responsible for 5.5% of all cancer cases and approximately 60% of GC cases, making this infection the primary cause of GC worldwide and the second leading defined cause of malignancy after smoking (10, 13, 14).

## DISCUSSIONS

### Pathogenetic mechanisms of HP-induced carcinogenesis

In general, GC is the consequence of a multifactorial process involving host responses, specific host-microbe interactions, bacterial virulence, diet, and other environmental factors. Although the mechanisms of HP-induced carcinogenesis have not been fully elucidated, inflammation is considered the most important and frequent factor in this process. Chronic inflammation is thought to induce cancer by increasing the production of reactive oxygen species, leading to oxidative stress, apoptosis of epithelial cells with a compensatory proliferative response of the remaining cells, and an increased risk of mutations in proliferating epithelial cells. In addition, HP affects DNA repair both in vivo and in vitro, causing epigenetic alterations in gastric epithelial cells. All these adaptive responses enhance cell survival and proliferation, leading to the acquisition of malignant characteris-



tics that enable the progression of precancerous gastric lesions, invasion, and metastasis (3, 12, 13, 15, 18, 25, 33, 34).

The importance of inflammation as a risk factor is confirmed by three complementary observations: (1) bacterial strains that induce the greatest inflammation have the strongest associations with malignancy; (2) host proinflammatory cytokine polymorphisms increase cancer risk; and (3) nonsteroidal anti-inflammatory agents reduce cancer risk (13, 24).

Other mechanisms in addition to inflammation have been identified in HP-related gastric carcinogenesis. HP interacts directly with epithelial cells, leading to protein modulation and gene activation, and damages parietal cells, thereby altering the maturation process of epithelial stem cell lineages (4, 13).

There are two important mechanisms through which HP can ultimately lead to intestinal-type GC:

1. *Indirect mechanisms through inflammatory processes.* Intestinal-type gastric adenocarcinoma represents the final stage of a long precancerous process known as Correa's cascade of multistep gastric carcinogenesis. The pathogenesis of GC involves a sequence of events that begins with superficial (non-atrophic) chronic gastritis induced by HP, progressing to chronic atrophic gastritis (initially limited to the gastric corpus or antrum, and later becoming multifocal), gastric intestinal metaplasia (initially "complete" and then "incomplete"), gastric epithelial dysplasia (initially low-grade and later high-grade), and finally GC. Progression to gastric epithelial dysplasia and GC is thought to involve processes that no longer require the presence of HP (7, 24, 25, 33, 34, 35).

Persistent HP infection is maintained through a variety of mechanisms: HP can protect itself from toxic substances such as reactive oxygen species, induce macrophage apoptosis, and increase the expression of proinflammatory factors. Aberrant DNA methylation in gastric epithelial cells occurs in parallel with the HP-associated inflammatory response (8).

2. *Direct mechanisms of HP on gastric epithelial cells through the toxic action of virulence factors.* Mutations in cell cycle regulatory genes, deficiencies in DNA repair mechanisms, loss of cellular adhesive properties, and epigenetic changes can alter cellular behavior, leading to cellular autonomy and malignant transformation (1, 8, 16, 22, 25, 27, 28, 34).

Two widely studied virulence factors are the CagA and VacA cytotoxins, which play a crucial role in the pathogenicity of HP infection. These virulent strains contribute to gastric carcinogenesis through their immunosuppressive activities, promotion of bacterial survival, and maintenance of gastric inflammation, and are associated with precancerous gastric lesions and progression to a malignant phenotype (4, 12, 19, 20, 25, 28).

Urease, which is abundantly secreted by HP, influences the host response beyond its enzymatic action by activating monocytes and polymorphonuclear leukocytes, leading to inflammation and epitheli-

al damage. Adhesins (BabA, SabA) are bacterial surface proteins that contribute to the attachment of the bacterium to host cells. HP adhesion to the gastric epithelium is a key step in the colonization of the gastric mucosa (28).

Thus, research suggests that the oncogenic effects of HP infection may occur through a variety of mechanisms, including the indirect inflammatory effects of HP on the gastric mucosa and the direct epigenetic effects of HP on epithelial cells. During HP infection, a combination of environmental and genetic factors plays a crucial role in the progression of gastric disease and the development of GC (8, 34, 36). However, it should be noted that despite the large number of studies dedicated to HP, it is still unclear whether the infection is involved only in the initiation of the gastric tumor process or whether it can also affect tumor progression mechanisms (11).

### Cofactors in carcinogenesis

Although half of the world's population is infected with HP, only a minority of individuals (an estimated 1-3%) are exposed over their lifetime to progression toward GC. When only middle-aged adults are considered, the risk of cancer becomes more substantial. For example, in prospective studies conducted in Asia, between 3% and 6% of HP-infected subjects developed GC within a decade (12, 13, 28).

It is currently accepted that bacterial virulence factors of the HP strain are the most important in GC development. However, as in other infections, there are environmental and host genetic factors that predispose to and interact with certain pathogenic strain factors, such as the CagA cytotoxin. HP may harbor pathogenic factors such as cytotoxins and a pathogenicity island (cag) that encodes the secretion of the bacterial oncoprotein CagA, which is involved in the carcinogenic process in addition to the inflammation it generates. Studies have found that approximately 60% of HP bacterial strains possess the CagA cytotoxin (3, 15, 17, 21, 25, 28, 33).

There is evidence that HP may not be the only microbe responsible for the development of GC, as this bacterium diminishes as atrophy progresses and practically disappears in areas of tumor tissue. HP does not colonize areas of cancer, intestinal metaplasia, or atrophy, and there is evidence that as advanced gastric disease develops, the bacterium may disappear from the stomach. These findings may indicate that HP infection is not essential at all stages of GC development and that the mechanism may differ from the progression of chronic atrophic gastritis and gastric intestinal metaplasia (1). Oral microbiota is also involved through various mechanisms, such as anti-apoptotic activity, immune system suppression, initiation of chronic inflammation, and the development of mutations (16).

HP infection alone is not sufficient for the development of GC. The bacterium has a synergistic relationship with host factors, primarily immune and reparative responses, and environmental factors, which amplify the risk of subsequent neoplastic transformation. After bacterial genetics, the most important factor influencing carcinogenesis is likely host genetics. Single nucleotide polymorphisms in interleu-

kin genes (IL-1 $\beta$ , IL-1-RN2, IL-8, IL-10, TNF- $\alpha$ ) are genetic susceptibility factors associated with individual or familial susceptibility to HP-mediated carcinogenesis (3, 8, 13, 15, 19, 33, 34). Individuals with the IL-1 $\beta$ -31C gene and the IL-1 receptor antagonist gene (IL-1-RN2) are more likely to develop HP-induced gastric atrophy, gastric cancer, or hypochlorhydria (16, 18, 19, 25).

The risk factors associated with the development of precancerous gastric lesions are practically similar to those associated with GC. Environmental factors such as iron deficiency or dietary habits (consumption of salt-preserved foods and N-nitroso compounds, and a diet low in micronutrients from fresh fruits and vegetables), smoking, and alcohol consumption damage the gastric mucosa, facilitate HP infection and persistence, and increase susceptibility to tumorigenesis. In addition, bacterial factors interacting with environmental factors further increase the risk of GC (13, 17, 18, 24, 27, 33).

## CONCLUSIONS

1. *Helicobacter pylori* infection is found on average in 50% of the population across all regions of the world. The prevalence of this infection varies considerably worldwide depending on the geographical distribution and socioeconomic status of the population – higher rates are observed in developing countries (up to 80%) compared to economically developed countries (up to 30%).
2. *Helicobacter pylori* is a heterogeneous species that can harbor virulence factors, the most important being urease, adhesins (BabA and SabA), and cytotoxins (CagA and VacA), which play a crucial role in the pathogenicity of the infection and are involved in the carcinogenic process. These virulent strains contribute to gastric carcinogenesis through their immunosuppressive activities, promotion of bacterial survival, and maintenance of gastric inflammation, and are associated with precancerous gastric lesions and progression to a malignant phenotype.
3. The etiology of gastric cancer is complex and multifactorial, involving environmental and host-related factors, as well as genetic and epigenetic changes. *Helicobacter pylori* infection requires multiple known mechanisms (and likely others yet to be discovered) to induce the onset and progression of gastric cancer, making it the most important risk factor in the pathogenesis of this malignancy.
4. Inflammation is the most important and frequent factor in the process of *Helicobacter pylori*-induced carcinogenesis. Chronic inflammation induces cancer by increasing the production of reactive oxygen species, which leads to oxidative stress, apoptosis of epithelial cells with a compensatory proliferative response of the remaining cells, and an increased risk of mutations in proliferating epithelial cells. In addition, *Helicobacter pylori* affects DNA repair, causing epigenetic alterations in gastric epithelial cells. All these adaptive responses enhance cell survival and proliferation, leading to the acquisition of malignant characteristics that enable the progression of precancerous gastric lesions, invasion, and metastasis.



5. The pathogenesis of gastric cancer involves a sequence of events that begins with superficial (non-atrophic) chronic gastritis induced by *Helicobacter pylori*, progressing to chronic atrophic gastritis (initially limited to the gastric corpus or antrum, and later becoming multifocal), gastric intestinal metaplasia (initially “complete” and then “incomplete”), gastric epithelial dysplasia (initially low-grade and later high-grade), and finally gastric cancer.
6. *Helicobacter pylori* eradication therapy can provide long-term protection against gastric cancer in high-risk populations, particularly in healthy, asymptomatic infected individuals without advanced gastric lesions at baseline. Eradication of *Helicobacter pylori* in patients with advanced preneoplastic gastric lesions does not prevent the development of gastric cancer, and endoscopic surveillance must always be performed.

**CONFLICT OF INTEREST** There is no conflict of interest.

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